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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,534	05/31/2000	BARBARA ENSOLI	11340-003-999	9400

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	
MAIL DATE	**DELIVERY MODE**
07/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/555,534	ENSOLI, BARBARA	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *169-178 and 192* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,63,65,66,68,69,89-103,105-112,114,116,117,119,121-128,142-168 and 179-191* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 5/1/07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 62,63,65,66,68,69,89-103,105-112,114,116,117,119,121-128 and 142-192.

DETAILED ACTION

This Office Action is in response to the amendment filed on 01 May 2007. Claims 1-61, 64, 67, 70-88, 104, 113, 115, 118, 120 and 129-141 have been cancelled. Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-128, 142-192 are pending. Claims 169-178 and 192 are withdrawn. Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-128, 142-168 and 179-191 are under final rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168, and 179-191 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in response to Applicant's amendment, which limits the Tat mutant to SEQ ID NO:7, 8, or 9 and limiting the Tat fragment to SEQ ID NO:16 or 17.

The rejection of claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168, and 179-191 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification commensurate in scope is **maintained**.

The instant claims are drawn to a composition comprising an isolated Tat protein, fragment of SEQ ID NO:16 or 17, or mutant of SEQ ID NO:7, 8 or 9 in combination with a pharmaceutically acceptable carrier or excipients, wherein said isolated Tat protein is biologically active, and wherein said composition is pharmaceutically acceptable for administration to a human.

Examiner's rejection in the Action mailed on 01 November 2006 is as follows:

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168, and 179-191 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a composition comprising an isolated Tat protein, does not reasonably provide enablement for a Tat protein composition that is pharmaceutically acceptable for administration to a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP §2164.01(a)):

Nature of the invention. The claims are drawn to a biologically active Tat protein-based HIV-vaccine. Furthermore, the specification clearly states on page 1 that the present invention refers to a prophylactic and/or therapeutic vaccine anti-HIV, anti-AIDS and against tumors and syndromes associated with HIV infection. Therefore, the instant claims, when read in light of the specification, would lead one skilled in the art to conclude that the instant invention is clearly directed towards HIV vaccines.

Breadth of the claims. The broad claims with the limitation "pharmaceutically acceptable for administration to a human" encompass vaccine compositions for preventing HIV in humans, and the limitation "fragment or mutant" encompasses a genus of inordinate number of HIV Tat species as small as three amino acids.

Working examples. A working example of monkeys is disclosed in the specification.

Guidance in the specification. The amount of direction is limited to a macaque model, wherein the administration of HIV Tat resulted in antigen-specific antibody response and CTL response (spec. example 5) and antigen-specific T-cell activation as determined by in vitro assays of PBMC samples (spec. example 4). This test is unreliable in detecting minority HIV-1 variants in the virus population of a patient. Resistant mutants may not persist at detectable levels in the absence of drug selection pressure (Martinez-Picado, 1998, pages 84, 85, and 87), which increases the complexity in extrapolating from *in vitro* to *in vivo* test results and even from one animal model to humans. Even though the specification teaches the generation of natural immune

response in monkeys, the disclosure does not relate to protection against any strain and/or clade of HIV-1 in humans.

State of the prior art. At the time the invention was made, a pharmaceutical HIV-vaccine comprising Tat protein, fragment or mutant is not considered routine in the art.

Predictability of the art. The state of the art of development of HIV vaccine is highly unpredictable, since HIV replicates rapidly with a high mutational frequency and creates diverse 'quasi-species', which are favored by the Darwinian selective pressures. Therefore, efforts to develop effective treatments and vaccines must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

Experimental HIV-1 infection *in vivo* and *in vitro* both suffer from the limitation that the *in vitro* amplification of HIV-1, which is required to prepare virus stocks for in vitro or in vivo infectivity experiments, impose a genetic selection that results in a spectrum of variants present in the clinical specimens used to establish the culture (Kusumi et al., 1992; Meyerhans et al., 1989). Because of these uncertainties, and even greater uncertainties related to the amount of virus transmitted, the site and cell type involved in initial replication, and the kinetics of virus dissemination, the ability of currently available in vitro or in vivo assays to reliably predict vaccine efficacy is questionable. Small trials in "populations with low rates of infection and minimally sized placebo control groups do not have sufficient statistical power to confirm or refute vaccine efficacy.

A natural immune response, consisting of antibody response and viral-specific CD8+ cellular response as measured in the instant application, is not effective because HIV has evolved a number of evasion strategies: selection for genetic variants that are antigenic escapes variants; inherent resistance to antibody-mediated neutralization; down regulation of major histocompatibility class I molecules from the surface of infected cells by Nef; and destruction of viral-specific CD4+ T helper cells. It is well established in the art that CD8+ cellular responses, or cytotoxic T lymphocyte (CTL) responses select for viral escape variants that are resistant to immune recognition, but the fate of these escape mutants after transmission to new hosts is unclear. If CTL escape mutations can be reserved after transmission of HIV, HIV escape variants might be propagated in populations. Over time, epitopes targeted by CTL-based vaccines could be lost from circulating virus strains, rendering vaccines that are based on single or consensus strains ineffective. The main problem with HIV vaccines is that there has not been a solution to overcome the enormous sequence heterogeneity of HIV-1 (see Altman et al., 2004; Desrosiers, 2004; Friedrich et al., 2004; and Leslie et al., 2004).

Amount of experimentation necessary. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In the instant case, a pharmaceutical HIV vaccine comprising an isolated Tat protein is not considered routine

in the art and, without sufficient guidance to its clinical efficacy, the experimentation left to those skilled in the art is undue or unreasonable under the circumstances.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed product.

Applicant argues that the claimed composition need not be used as an HIV vaccine for successful treatment or prevention of HIV infection in humans and instead may be used to induce an immune response against biologically active Tat. Applicant further argues the clinical trial showed that a claimed composition was safe and well tolerated in all subjects in the preventative and therapeutic phase I trials.

Applicant's arguments have been fully considered but are not persuasive. While Applicant's statement that the claimed composition has alternative use than an HIV vaccine is true, the alternative intended use limitation of inducing an immune response is not a feature recited in the claims. In fact, the instant claims specifically limit the composition to be "pharmaceutically acceptable for administration to a human," which excludes the immune induction aspect of the invention as asserted by the Applicant. Secondly, the instant specification does not enable the claimed composition because Applicant's own disclosure of the invention indicates the use of PMSF or HPLC in the preparation of the Tat protein (page 25, line 5-7 and 15), which, according to Applicant, render the composition not pharmaceutically acceptable for administration to a human because the TFA and acetonitrile from the HPLC step and the PMSF are very toxic (see page 15-17 of the response filed on 01 May 2007). Therefore, Applicant's own argument negates her assertion about the safety and the positive clinical outcome of the claimed composition.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, and 186 under 35 U.S.C. §102(b) as being anticipated by Chang *et al.* is **maintained**.

The instant claims read on a composition comprising an isolated Tat protein in combination with a pharmaceutically acceptable carrier or excipients, wherein said isolated Tat protein is biologically active.

Chang *et al.* teach a composition comprising fully biologically active HIV Tat proteins, which are stored by lyophilization and resuspended in degassed buffer, PBS containing 0.1% BSA and 0.1 mM DTT before use (page 1424, left column, Tat protein and anti-Tat antibody, Purification of recombinant Tat protein by heparin affinity chromatography).

Applicant argues that Chang *et al.* do not disclose that the resulting Tat composition is pharmaceutically acceptable for administration to a human. The first purification method of Chang may result in a Tat composition containing toxic solvents, acetonitrile and TFA, from the HPLC, and the second purification method includes the neurotoxic PMSF.

Applicant's arguments have been fully considered but are not persuasive. The specification of the instant application is also silent on whether the final Tat composition is rid of the HPLC solvents. The specification even cites the Chang reference and specifically states the inclusion of PMSF in the heparin affinity purification method. See page 25, line 5-7 and line 15. Examiner has stated this reason for maintaining the rejection over Chang in the Office Action (on top of page 3) mailed on 01 November 2006. Applicant has failed to address this issue in the response while alleging that the Chang reference does not teach a pharmaceutical Tat composition for administration to humans. In conclusion, Applicant has not provided any objective evidence to support the assertion that the Chang composition is not "pharmaceutically acceptable for administration to a human."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94, 106, 107, 114, 119, 128, 142-150, 152,153, 155-159,161,162, 164-168, 179-183, 185, 186 and 189 under 35 U.S.C. §103(a) as obvious over Chang *et al.* in view of Heiman *et al.* is **maintained**

for the same reason as above because applicant presented the same arguments as for the rejection as anticipation by Chang *et al.*

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-95, 97, 101-103, 105-111,116, 117, 121,122, 128, 142-168, 179-187, 190, and 191 under 35 U.S.C. §103(a) as obvious over Chang *et al.* in view of Vogel *et al.* is **maintained** for the same reason as above because applicant presented the same arguments as for the rejection as anticipation by Chang *et al.*

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94, 99, 106, 107, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185 and 186 under 35 U.S.C. §103(a) as obvious over Chang *et al.* in view of Castignolles *et al.* is **maintained** likewise for the same reason as above.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94,100, 106, 107, 128, 142-150, 152, 153, 155-159, 161,162, 164-168, 179-183, 185 and 186 under 35 U.S.C. §103(a) as obvious over Chang *et al.* in view of Ramshaw *et al.* is **maintained** likewise for the same reason as above.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 112, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168,179-183, 185, 186, and 188 under 35 U.S.C. §103(a) as obvious over Chang *et al.* in view of Livingston *et al.* is **maintained** likewise for the same reason as above.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94, 106, 107, 123, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185 and 186 under 35 U.S.C.

§103(a) as obvious over Chang *et al.* in view of Barry *et al.* is **maintained** likewise for the same reason as above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
18 July 2007

Louise Humphrey, Ph.D.
Assistant Examiner